Sustained siRNA production from human MSC to treat Huntingtons Disease and other neurodegenerative disorders

Grant Award Details

Sustained siRNA production from human MSC to treat Huntingtons Disease and other neurodegenerative disorders

Grant Type: Early Translational I

Grant Number: TR1-01257

Project Objective: This is a Development Candidate project with the goal to develop an MSC-based system for the delivery of anti-huntingtin siRNA into the brain of Huntington's patients.

Investigator:

Name:	Jan Nolta
Institution:	University of California, Davis
Type:	PI

Disease Focus: Huntington's Disease, Neurological Disorders

Human Stem Cell Use: Adult Stem Cell, Embryonic Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $2,615,674

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Sustained siRNA production from human MSC to treat Huntingtons Disease and other neurodegenerative disorders

Public Abstract:

One in every ten thousand people in the USA have Huntington's Disease, and it impacts many more. Multiple generations within a family can inherit the disease, resulting in escalating health care costs and draining family resources. This highly devastating and fatal disease touches all races and socioeconomic levels, and there are currently no cures. Screening for the mutant HD gene is available, but the at-risk children of an affected parent often do not wish to be tested since there are currently no early prevention strategies or effective treatments.

HD is a challenging disease to treat. Not only do the affected, dying neurons need to be salvaged or replaced, but also the levels of the toxic mutant protein must be diminished to prevent further neural damage and to halt progression of the movement disorders and physical and mental decline that is associated with HD.

Our application is focused on developing a safe and effective therapeutic strategy to reduce levels of the harmful mutant protein in damaged or at-risk neurons. We are using an RNA interference strategy – "small interfering RNA (siRNA)" to prevent the mutant protein from being produced in the cell. This strategy has been shown to be highly effective in animal models of HD. However, the inability to deliver the therapeutic molecules into the human brain in a robust and durable manner has thwarted scale-up of this potentially curative therapy into human trials. We are using mesenchymal stem cells, the "paramedics of the body", to deliver the therapeutic siRNA directly into damaged cells. We have discovered that these stem cells are remarkably effective delivery vehicles, moving robustly through the tissue and infusing therapeutic molecules into each damaged cell that they contact. Thus we are utilizing nature's own paramedic system, but we are arming them with a new tool to also reduce mutant protein levels. Our novel system will allow the therapy to be carefully tested in preparation for future human cellular therapy trials for HD.

The significance of our studies is very high because there are currently no treatments to diminish the amount of toxic mutant htt protein in the neurons of patients affected by Huntington's Disease. There are no cures or successful clinical trials for HD. Our therapeutic strategy is initially examining models to treat HD, since the need is so acute. But this biological delivery system could also be used, in the future, for other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA1), Alzheimer's Disease, and some forms of Parkinson's Disease, where reduction of the levels of a mutant or disease-activating protein could be curative.

Development of this novel stem cell therapeutic and effective siRNA delivery system is extremely important for the community of HD and neurodegenerative disease researchers, patients, and families.

Statement of Benefit to California:

It is estimated that one in 10,000 CA residents have Huntington's Disease (HD). While the financial burden of Huntington's Disease is estimated to be in the billions, the emotional burden on the friends and families of HD patients is immeasurable. Health care costs are extremely high for HD patients due to the decline in both body and mind. The lost ability of HD patients to remain in the CA workforce and to support their families causes additional financial strain on the state's economy. HD is inherited as an autosomal dominant trait, which means that 50% of the children of an HD patient will inherit the disease and will in turn pass it on to 50% of their children. Individuals diagnosed through genetic testing are at risk of losing insurance coverage. Since there are currently no cures or successful clinical trials for HD, many are reluctant to be tested. The proposed project is designed in an effort to reach out to these individuals who, given that HD is given an orphan disease designation, may feel that they are completely forgotten and thus have little or no hope for their future or that of their families.

To combat this devastating disease, we are using an RNA interference strategy, "small interfering RNA (siRNA)," to prevent the mutant htt protein from being produced in the cell. This strategy has been shown to be highly effective in animal models of HD. However the siRNA needs to be delivered to the brain or central nervous system in a continual manner, to destroy the toxic gene products as they are produced. There are currently no methods to infuse or produce siRNA in the brain, in a safe and sustained manner. Therefore the practical clinical use of this dramatically effective potential therapeutic application is currently thwarted.

Here we propose a solution, using adult mesenchymal stem cells (MSC) modified to infuse siRNA directly into diseased or at-risk neurons in the striata of HD patients, to decrease the levels of the toxic mutant htt protein. MSC are known as the "paramedics of the body" and have been demonstrated through clinical trials to be safe and to have curative effects on damaged tissue. Even without the modification to reduce the mutant protein levels, the infused MSC will help repair the damaged brain tissue by promoting endogenous neuronal growth through secreted growth factors, secreting anti-apoptotic factors, and regulating inflammation.

Our therapeutic strategy will initially examine models to treat HD, since the need is so acute. But our biological delivery system could also be applied to other neurodegenerative disorders such as ALS, some forms of Parkinson's Disease, and Alzheimer's Disease, by using siRNA to interfere with key pathways in development of the pathology. This would be the first cellular therapy for HD patients and would have a major impact on those affected in California. In addition, the methods that we are developing will have far-reaching effects for other neurodegenerative disorders.
